UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,569	05/02/2002	Audrey Goddard	P3230R1C49	9761

30313 7590 05/16/2005

KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

EXAMINER	
HUNNICUTT, RACHEL KAPUST	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 05/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,569	GODDARD ET AL.	
	Examiner	Art Unit	
	Rachel K. Hunnicutt	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8 and 11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0405*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

Applicant's amendment filed April 7, 2005 is acknowledged. Claims 1-3 and 9-10 have been canceled. Claims 4-8 and 12-13 have been amended. Claims 14-17 are new. Claims 4-8 and 11-17 are pending and under consideration. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claim Rejections/Objections Withdrawn

The objection to the specification regarding the use of trademarks is withdrawn in response to Applicants' amendment to the specification.

The objection to the specification for containing an embedded hyperlink is withdrawn in response to Applicants' amendment to the specification.

The rejection of claims 1-3 and 9-10 under 35 U.S.C. 101 as not be supported by either a specific and substantial asserted utility or a well-established utility is withdrawn in response to Applicants' cancellation of these claims.

The rejection of claims 4-6 and 12-13 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in response to Applicants' amendment to the claims. The rejection of claims 1-3 and 10 under 35 U.S.C. 112, second paragraph, is withdrawn in response to Applicants' cancellation of the claim.

The rejection of claims 1-3 and 9-10 under 35 U.S.C. 112, first paragraph, as not being enabled because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility, is withdrawn in response to Applicants' cancellation of these claims.

The rejection of claims 1-3 under 35 U.S.C. 112, first paragraph, because the specification, were it enabling for an isolated polypeptide comprising SEQ ID NO: 64, would still not reasonably provide enablement for polypeptides having at least 80%, 85%, or 90% amino acid sequence identity to the polypeptide of SEQ ID NO: 64, is withdrawn in response to Applicants' cancellation of these claims.

The rejection of claims 1-3 under 35 U.S.C. 112, first paragraph, for not complying with the written description requirement, is withdrawn in response to Applicants' cancellation of these claims.

The rejection of claims 1-3 under 35 U.S.C. 102(a) as being anticipated by Oka *et al.* (NCBI Accession No. BAA88132) is withdrawn in response to Applicants' cancellation of these claims.

The rejection of claims 1-3 under 35 U.S.C. 102(b) as being anticipated by Janer *et al.* (NCBI Accession No. AC006163) is withdrawn in response to Applicants' cancellation of these claims.

Rejections Maintained

Claim Rejections - 35 USC § 101

The rejection of claims 4-8 and 12-13 under 35 U.S.C. 101 is maintained for reasons of record on p. 2-4 of the office action of paper no. 0105 and is applied to new claims 14-17.

Applicants argue that mRNA for the PRO3566 polypeptide is more highly expressed in normal skin compared to melanoma tumor, and in esophageal tumor compared to normal esophagus (p. 16 of the response). Applicants further argue that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. Applicants refer to a declaration of J. Christopher Grimaldi (Exhibit 1) and argue that "the biological significance of the data, or the role of PRO3566 in cancer, is not necessary to use the claimed polypeptides as cancer diagnostic tools" (p. 16 of the response). Applicants argue

that Exhibit 1 teaches that the DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. Grimaldi states in section 6 that "I conducted a semi-quantitative analysis of the expression of the DNA sequences of interest in normal versus tumor tissues. Expression levels were graded according to a scale of +, -, and +/- to indicate the amount of the specific signal detected. Using the widely accepted technique of PCR, it was determined whether the polynucleotides tested were more highly expressed, less expressed, or whether expression remained the same in tumor tissue as compared to its normal counterpart. Because this technique relies on the visual detection of ethidium bromide staining of PCR products on agarose gels, it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA."

Furthermore, in another declaration of J. Christopher Grimaldi (Exhibit 4), Grimaldi states that when a gene is overexpressed, the gene product or polypeptide will also be overexpressed (p. 19 of response). The declaration of Dr. Paul Polakis avers that mRNA levels typically correlate with an increase in abundance of the encoded protein (p. 20 of response). Applicants further cite Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* in support of the argument that in the vast majority of cases, the combined teachings of the art teach that gene amplification influences gene expression and that gene expression influences protein levels. In addition, Applicants refer to the declaration of Dr. Ashkenazi and cited references Hanna and Mornin who teach that even if higher levels of mRNA do not correlate with an increase in abundance of the encoded protein, that type of information is also useful in diagnosing and treating patients.

Applicants' arguments have been fully considered but have not been found to be persuasive. A utility of being a diagnostic target for melanoma or esophageal tumors is a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use. This is not a substantial utility. In Example 30, Applicants teach that PRO3566 was overexpressed in normal skin and esophageal tumor than in melanoma tumor and normal esophagus tissue. There is no guidance in the specification as to how high the levels of overexpression are. There is no information in the specification as to the differences in expression or whether the results were statistically significant. Applicants have provided no indication of the nature or number of samples that were used. The declaration of Grimaldi does not teach the level of reproducibility or the level of reliability of the results. If a clinician took a

skin or esophageal tissue sample from a patient with suspected melanoma or esophageal cancer, what is the likelihood that when compared with normal tissue, the level of PRO3566 from the patient would be higher or lower? How many samples would be needed? What sensitivity would be needed? Applicants have provided no indication of the nature or number of samples that were used.

The only thing Applicants teach is that the gene was "more highly expressed", and this does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any diseases. On p. 19 of the response, Applicants state that when a gene is overexpressed, the corresponding protein will generally also be overexpressed. However, Chen *et al.* teach that correlation between protein levels and mRNA expression can vary depending upon the protein (Chen *et al.* (2002), *Mol. Cell. Proteomics* 1.4: 304-313). Of 165 protein spots studied by Chen *et al.*, only 17% of the samples showed a statistically significant correlation between mRNA and protein (p. 311). Some of the proteins actually demonstrated a negative correlation with the mRNA expression values (p. 311). One skilled in the art would need to do further research to determine whether or not the PRO 3566 polypeptide levels increased or decreased significantly in the tumor samples. Such further research requirements make it clear that the asserted utility is not yet in currently available for, *i.e.* it is not substantial. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of skin and esophageal tissue that can be used, and other questions, the specification has not provided the invention in a form readily usable by the skilled artisan such that significant further experimentation is unnecessary.

Claim Rejections - 35 USC § 112

The rejection of claims 4-8 and 12-13 under 35 U.S.C. 112, first paragraph for lack of enablement because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, is maintained for reasons of record on p. 4-5 of paper no. 0105 and is applied to new claims 14-17.

The rejection of claims 4-5 and 12-13 under 35 U.S.C. 112, first paragraph, because the specification, were it enabling for an isolated polypeptide comprising SEQ ID NO: 64, would still not reasonably provide enablement for polypeptides having at least 95% or 99% amino acid sequence identity to the polypeptide of SEQ ID NO: 64, is maintained for reasons of record on p. 5-6 of paper no. 0105 and is applied to new claims 14-17.

Applicants argue that one skilled in the art would know how to make and use the claimed polypeptides, and Applicants have disclosed how to determine if the claimed polypeptides or encoding nucleic acids are differentially expressed in melanoma tumors or esophageal tumors compared to normal skin or normal esophagus (p. 27).

Applicants' arguments have been fully considered but have not been found to be persuasive. Being differentially expressed in melanomas or esophageal tumors is not a functional limitation. Rather, it is a characteristic of an individual sequence. Even if the specification provided support for diagnosing melanomas or esophageal tumors with PRO3566, the skilled artisan would not know how to use polypeptides having sequences at least 95% or 99% sequence identity to PRO4381. Such sequences are not taught to be differentially expressed in melanomas or esophageal tumors. One skilled in the art would not know how to engineer a sequence such that it is overexpressed in certain tissues.

Claims 14-17 have the limitation "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 64 in skin tissue or esophagus samples. Again, this is not a functional limitation. Applicants have not specified certain regions of SEQ ID NO: 64 which contain epitopes particular to an anti-PRO3566 antibody. This is merely another means for claiming a polypeptide having a percent identity to SEQ ID NO: 64. One skilled in the art would not know how to make a protein at least 95% or 99% identical to SEQ ID NO: 64 such that antibodies raised against the sequence would specifically recognize SEQ ID NO: 64 and not other sequences 95% or 99% identical to SEQ ID NO: 64.

The rejection of claims 4-5 and 12-13 under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement, is maintained for reasons of record on p. 6-7 of paper no. 0105 and applied to new claims 14-17.

Applicants argue that the claimed polypeptides are not defined only by sequence identity, but that they now recite a specific functional limitations that the polypeptide is more highly expressed in normal skin and esophageal tumor than in melanomas or esophageal tumors or the polypeptides can be used to raise antibodies that recognize SEQ ID NO: 64. Applicants argue that based on the high percentage of sequence identity and the described method of detecting and quantifying overexpression in tumors, one skilled in the art would have known at the time of the invention that Applicants had possession of the claimed polypeptides.

Applicants' arguments have been fully considered but have not been found to be persuasive. As stated above, the claims have no functional limitations. In addition, the specification does not provide a utility or function for PRO3566. The claimed polypeptide sequences may have functions and structures which differ greatly from that of PRO3566, therefore one of skill in the art would not be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Claim Rejections - 35 USC § 102

The rejection of claims 4 and 5 under 35 U.S.C. 102(a) as being anticipated by Oka *et al.* is maintained for reasons of record on p. 8 of paper no. 0105 and applied to new claims 14 and 15. The declaration filed on April 7, 2005 under 37 CFR 1.131 has been considered but is ineffective to overcome the Oka *et al.* reference. In order to be effective, the declaration must be signed by all of the inventors. Oka *et al.* teach a sequence which is 99% identical to SEQ ID NO: 64. Thus, claims 4-5 and 14-15 are anticipated by Oka *et al.*

The rejection of claim 4 under 35 U.S.C. 102(b) as being anticipated by Janer *et al.* is maintained for reasons of record on p. 8 of paper no. 0105 and applied to new claim 14.

Applicants argue that Janer *et al.* do not provide the amino acid sequence of SEQ ID NO: 64 and Janer *et al.* do not describe the coding region of the sequence that encodes SEQ ID NO: 64 (p. 31 of the response). Applicants' arguments have been fully considered but have not been found to be persuasive. The sequence as taught by Janer *et al.* encodes a polypeptide 98% identical to SEQ ID NO: 64. This is an inherent feature of the sequence as taught by Janer *et al.*

Conclusion

NO CLAIMS ARE ALLOWED.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel K. Hunnicutt whose telephone number is (571) 272-0886. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RKH
5/4/05

JANET ANDRES
PRIMARY EXAMINER